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Disease-a-Month

Disorders of Menstruation

JOSEPH ROGERS

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Disorders of Menstruation

JOSEPH ROGERS

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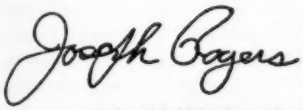

received his M.D. degree from the Harvard Medical School in 1941, served residencies in medicine at the Boston City Hospital and New England Center Hospital and is an internist interested in the medical aspects of gynecology. He is a Fellow of the American College of Physicians and a member of the American Society for the Study of Sterility. He is Physician at the New England Center Hospital and Assistant Professor of Medicine and Lecturer in Gynecology at Tufts University School of Medicine.

MENSTRUATION is a complex process involving relationships between the several endocrine glands, changes in the endometrium of the uterus and changes in other portions of the body. Our knowledge of the details is incomplete but a brief review of what is known of menstrual physiology is important in our attempts to understand the various clinical problems commonly encountered.

PHYSIOLOGY OF MENSTRUATION

The pituitary hormones directly concerned with menstruation are the follicle-stimulating hormone (FSH), the luteinizing hormone (LH) and luteotropin (LTH). It is generally held that these gonadotropins are separate entities and not one hormone with different actions. The follicle-stimulating hormone is responsible for the growth and development of the ovarian follicle (29). It is secreted throughout the cycle by a recognizable type of basophilic cell of the anterior pituitary (43). As the primordial follicle migrates from beneath the tunica albuginea toward the interior of the ovary, the cells surrounding the ovum, called granulosa cells, proliferate and a crescentic cavity is formed by

liquefaction of a portion of the granulosa cells. The accumulation of fluid in this cavity slowly distends the follicle. The connective tissue surrounding the follicle becomes differentiated into the theca interna and becomes rich in epithelioid cells and capillaries. It is these epithelioid cells that are thought to be the main source of estrogen. Until the stage of antrum formation, follicular development proceeds independently of the pituitary but further development is under control of the follicle-stimulating hormone.

The luteinizing hormone is secreted by another type of basophilic cell of the anterior pituitary throughout the menstrual cycle and is probably the hormone responsible for ovulation. Before the midcycle there is an increase in the amount of LH secreted and under its influence rupture of the ovarian follicle and ovulation occur. Following the discharge of the ovum, the collapsed follicle undergoes transformation into the corpus luteum. The theca interna proliferates and the granulosa cells are transformed into granulosa lutein cells which elaborate progesterone, the hormone of the corpus luteum. Estrogen is also produced by the corpus luteum.

A third gonadotropic hormone, luteotropin, has been shown in the rat to be necessary for the maintenance of a functioning corpus luteum (2) and probably has a similar role in the human female.

Both estrogen and progesterone have important reciprocal actions with the gonadotropins. Estrogen in small amounts effects release of FSH from the pituitary but in increasing amounts inhibits FSH production. Estrogen stimulates the release of luteinizing hormone and probably of luteotropin. As FSH acts to increase follicle development and estrogen production, the increasing secretion of estrogen acts to diminish further production of FSH. Similarly, progesterone has a reciprocal reaction with luteinizing hormone. In the rat, daily administration of progesterone appears to suppress LH secretion but when estrogen levels are elevated progesterone has been shown to effect release of LH (15).

The major estrogenic steroids are 17 beta estradiol, estrone and estriol. The estrogens are not stored in the body but are utilized, inactivated or excreted almost as rapidly as they form.

Between 50 and 75% of the estrogens in peripheral blood are bound in some way to plasma proteins and about 50% are conjugated as sulfates or glucuronates (41). Numerous observations indicate that the liver is the most important site of estrogen metabolism. The chief effect of estrogen is the production of a proliferative endometrium. The vaginal epithelium proliferates, glycogen is deposited in the epithelial cells and the vaginal secretion becomes more acid. The cervical epithelium also proliferates and a thin, watery mucus is secreted by the cervical glands. The tubal epithelium increases in height and reaches maximal secretory activity at the time of ovulation. Other actions of estrogen consist of development of the breast, thickening of the skin and the production of increased pigmentation, particularly in the region of the mammary areolae. Estrogens produce increased proliferation of the buccal and gingival membranes, inhibit linear bone growth and accelerate epiphyseal closure. Estrogens cause slight retention of nitrogen, calcium, phosphorus, sodium, chloride and water (55).

The primary action of progesterone is the conversion of a proliferative endometrium to a secretory endometrium suitable for the implantation of the fertilized ovum. Progesterone has little or no effect on an endometrium not primed with estrogen. This observation is put to clinical use in the administration of progesterone to women with amenorrhea. If bleeding does not occur on cessation it indicates lack of sufficient estrogen to stimulate the endometrium. Withdrawal bleeding following progesterone can be accepted as evidence of previous adequate estrogen effect.

The chief urinary metabolites of progesterone are pregnanediol and pregnenolone. The site of conversion of progesterone to pregnanediol is probably the liver. It is excreted in the urine conjugated with glucuronic acid. Numerous methods of measuring urinary pregnanediol either as the complex or in the free state have been developed and the procedure is frequently used as a test of ovulation (47).

The vascular changes in the uterus during the menstrual cycle are complex (4, 37). The initial events leading to bleeding are the withdrawal of an adequate growth stimulus, namely, estrogen and progesterone or estrogen alone.

Most American girls begin to menstruate between the ages of 11 and 16, the average age being about 13. There is a clear trend toward earlier onset of menstruation in both Europe and the United States (16). The widely held view that girls in tropical areas begin to menstruate earlier is not borne out by available evidence. The age of onset of a girl's menarche is likely to be similar to that of her mother's. In general, absence of menses in a girl of 17 should be investigated, but lack of periods prior to this time is usually best managed by a policy of watchful waiting. Many of the early menstrual cycles are anovulatory so that irregularity and amenorrhea are rather common events. It may take from 25 to 39 menstrual cycles prior to the establishment of a regular pattern. It has also been well established that infertility is common for the first two years following menarche due, presumably, to infrequent ovulation. Most women experience menstruation at about 28-day intervals but normal ovulatory cycles may occur at intervals ranging from 23 to 35 days (21). It is important in recording the history to make certain that the patient is dating her cycle correctly. The cycle length should be recorded as the number of days from the start of one menstrual period to the start of the next. Many women complaining of a short cycle will be found to be counting from the end of one period to the start of the next. Some women expect to menstruate on the same day of each month and may become concerned if they have more than one period in a calendar month. It is astonishing that many women consider it abnormal to have a period on the first of a month and a second starting on the 28th or 29th of the same month. It is convenient for the recording of the menstrual data to make a graph with the days of the month across the top and the months of the year along the side of the graph, providing a readily understandable chart. Bleeding normally lasts anywhere from three to seven days. There is, unfortunately, no accurate method for estimating the amount of blood loss on the basis of the history.

AMENORRHEA

Amenorrhea is usually defined as the absence of menstruation for at least three months. It is probably one of the more common gynecologic complaints for which women consult physicians.

The most frequent cause of amenorrhea in the healthy young woman is pregnancy and it is the rare physician who, at some time in his career, has not failed to consider this diagnosis. Amenorrhea, of course, is a symptom, and it is helpful when confronted with this clinical symptom to think in etiologic terms. The following classification is based on that proposed by Sturgis (53), who considered amenorrhea under uterine, ovarian, pituitary and hypothalamic causes.

Uterine Amenorrhea

Congenital absence of the uterus is a rare condition. Destruction of the uterus by radiation, extensive sepsis or tuberculosis may have occurred. A simple method of determining whether or not functioning endometrial tissue is present is the administration of an estrogen for 21 days. Bleeding six to seven days following estrogen withdrawal can be accepted as evidence of an endometrium capable of stimulation.

Ovarian Amenorrhea

Premature menopause.—A classic example of ovarian amenorrhea is the menopause in which there is first failure of ovulation, then decrease in estrogen production with resultant rise in gonadotropin excretion. In the woman over 40 this is a normal process. Occasionally women are seen, however, in whom ovarian failure occurs in the reproductive years. Diagnostic studies reveal evidence of hypo-estrogenism as determined by vaginal smear, elevated excretion of follicle-stimulating hormone and failure of progesterone to produce withdrawal bleeding. The cause of premature menopause is obscure. It is customary to treat such patients with estrogens given for 25 days with progesterone added from about day 21 to day 25, both hormones being withdrawn on day 25. Withdrawal bleeding will usually occur in five to seven days after medication is stopped. At the onset of bleeding, cyclic estrogen and progesterone is again administered, usually for a total of three cycles. Unfortunately, therapy in premature menopause is usually ineffective in bringing about further spontaneous periods. However, cyclic administration of estrogen is helpful in preventing premature atrophic changes in breast and reproductive tract.

OVARIAN AGENESIS AND TURNER'S SYNDROME.—Within the past 20 years, ovarian agenesis has been recognized as a clinical entity. In 1938, Turner (58) described seven young girls in whom short stature, sexual infantilism, webbing of the neck and cubitus valgus were the predominant clinical features. With the recording of other cases, the association of infantilism, webbing of the neck and cubitus valgus with absent or rudimentary ovaries became apparent and the term ovarian agenesis became identified with Turner's syndrome. Patients with ovarian agenesis without other congenital defects have been reported and it is perhaps well to distinguish these two categories of ovarian failure. Turner's (57) criteria have been stated as "short but not dwarfed stature, in an amenorrheic or at least hypogonadal girl, in the absence of a history of potentially castrating disease, with any one or more of certain congenital anomalies apparent at first glance." The term Turner's syndrome should then be used to indicate an association of one or more congenital defects with ovarian agenesis. The diminished or absent breast development, infantile genitalia, absent or deficient pubic hair are manifestations of estrogen deficiency rather than a congenital defect. Determination of urinary FSH will usually show a high level and vaginal smears will disclose marked estrogen deficiency. The most common congenital defects are webbing of the neck, cubitus valgus and ocular abnormalities.

Recent observations on determination of chromosomal sex have helped to clarify theories as to the etiology of ovarian agenesis. Examination of skin biopsies from females discloses that in a certain proportion of the cell nuclei a mass of chromatin is apparent along the lateral edge of the nucleus. This is usually not found in biopsies of male skin (40). Similar observations on smears from the buccal mucosa have been made and it is possible on examination of a blood smear to demonstrate "drum stick" projections in the nuclei of a small percentage of the polymorphonuclear leukocytes in blood from females but not in males. The application of such technics to patients with ovarian agenesis has led to the interesting observation that most appear to be genetically male rather than female (26). Jost (33) has shown that if the intrauterine male rabbit is castrated and then allowed to remain in utero until near the expected time of

parturition, the male fetus will develop female genital ducts and external genitalia. It is likely that many of the patients with ovarian agenesis are genetic males who for obscure reasons have suffered early failure of testicular development and for lack of the testes develop the external genital characteristics of the female. In keeping with these observations, the term gonadal dysgenesis has been suggested as being more accurate and appropriate than ovarian agenes s. At any rate, patients with gonadal dysgenesis have usually been raised as female and no useful purpose is served in acquainting either the patient or family with the fact that they may be chromosomal males. Furthermore, the significance of sex chromatin pattern has recently been thrown into question by the finding of a "female" distribution of chromatin in buccal smears from three patients with Klinefelter's syndrome in whom gonadal biopsy showed male gametogenesis (10). The psychologic effect of attempts at sex conversion are disastrous and in most of these instances attempts at development of secondary male characteristics would be unsuccessful. With proper administration of an estrogen such as stilbestrol 1 mg. a day for 30 days, followed by seven days without stilbestrol, this cycle being repeated indefinitely, periodic withdrawal bleeding, development of labia and increase in size of vagina, cervix, uterus and breasts will occur. Marriage and normal coitus become possible. The patient is, of course, incapable of conception and should be made aware of this fact before marriage. Osteoporosis may occur in patients with gonadal dysgenesis and estrogen tends to delay its progression or development. Estrogens may also delay "premature aging" of the skin in such patients. Cyclic use of estrogens should not be undertaken until it is clear that no further growth is occurring. After age 15 or 16 it is generally permissible to institute estrogenic therapy (49).

STEIN-LEVENTHAL SYNDROME.—Another disorder which has been recognized in the past two decades is the Stein-Leventhal syndrome. It probably is best considered as an ovarian abnormality although it has not been definitely established that the primary defect is ovarian. The condition was first described in 1935 by Stein and Leventhal (52), who reported large polycystic ovaries showing a thickened capsule in a group of women with obesity, hirsutism and amenorrhea. Pathologically, there is a thick

tunica albuginea, follicular cysts and hyperplasia of theca interna. It has been postulated that because of the thickened capsule, proper development of the follicle and ovulation is prevented. Numerous studies have failed to show any demonstrable endocrine cause, although it has been suggested that perhaps the pathologic findings are associated with an increased secretion of luteinizing hormone. The syndrome has been expanded to include instances in which excessive vaginal bleeding is the presenting symptom (31). In a significant number of patients, bilateral wedge resection of ovarian tissue has resulted in resumption of normal ovulatory menstruation and subsequent pregnancy. No rationale is apparent for the benefits attributed to this surgical procedure, yet wedge resection appears to be justified in certain instances when sterility is a problem. The fertility of the husband should, of course, be established prior to surgery. Increasing experience with the Stein-Leventhal syndrome indicates that many of the patients apparently aided by wedge resection will revert to their previous amenorrheic status. In some patients with adrenal hyperplasia or with functioning pituitary tumors, the pathologic picture of the ovaries may resemble that seen in the Stein-Leventhal syndrome, suggesting that the clinical syndrome may be due to adrenal, ovarian or perhaps even pituitary disorders.

Pituitary Amenorrhea

Sheehan's syndrome.—It is clear that disorders of the pituitary gland that lead to interference with formation or release of gonadotropins will result in amenorrhea. One of the more common instances of hypopituitarism is Sheehan's syndrome (51), in which infarct necrosis of the pituitary occurs in association with hemorrhagic accidents of pregnancy. The classic history is that of a woman who has had a severe hemorrhage at the time of delivery. Following recovery it may be noted that lactation does not occur and that the pubic hair which has been shaved fails to regrow. The axillary hair may become sparse, menstruation does not occur and the patient complains of being cold, listless and tired. Apathy is usually a prominent symptom. Examination will disclose absent or sparse pubic and axillary hair, a peculiar waxy pallor of the skin, atrophy of vaginal

mucosa and of the labia and perhaps atrophic changes in the breasts. Decrease in pigmentation may be observed if sufficient time has elapsed. Laboratory examination will show low FSH excretion in the urine, evidence of thyroid deficiency, and low excretion of 17-ketosteroids and 17-hydroxycorticosteroids. Vaginal smears show evidence of estrogen deficiency. Therapy with cortisone, thyroid and estrogens usually provides a dramatic favorable response. It is customary first to administer cortisone for about a month with addition of thyroid and estrogens later.

Rare instances occur in which there is demonstrable only a specific deficiency of gonadotropic hormone production. Some of these patients, if followed long enough, may develop evidence of loss of other pituitary hormones.

PITUITARY TUMORS.—Patients with pituitary tumors, acidophilic or chromophobe adenomas or craniopharyngiomas may first complain of amenorrhea and the amenorrhea may antedate the clinical demonstration of a pituitary lesion by several years. The finding of a pituitary lesion is sufficiently frequent to make skull films and confrontation visual fields an important part of the diagnostic study of the woman with amenorrhea. Treatment of the pituitary lesion, either by radiation or surgery, rarely results in re-establishment of periods. Probably substitution therapy with cyclic administration of estrogen is desirable, particularly in young women.

CHIARI-FROMMEL SYNDROME.—Recently, there has been considerable interest in lactation syndromes. Chiari, in 1852, first described the association of persistent lactation, amenorrhea and uterine atrophy following delivery. Frommel (18) 30 years later, again called attention to this syndrome which is referred to as the Chiari-Frommel syndrome and has been expanded to include nulliparous women who may have persistent galactorrhea, amenorrhea and varying degrees of atrophy of the reproductive organs. It has been shown recently that in such patients the urinary excretion of FSH is low (17). In the few instances in which it has been measured, there has been an increased excretion of luteotropic hormone. It is postulated that the syndrome is the result of increased luteotropic hormone excretion. In about a third of the patients, pituitary tumors are demonstrated. Treatment of this syndrome is unsatisfactory (23). Periodic

administration of an estrogen will result in withdrawal bleeding and partial suppression of lactation, but return of ovarian function does not occur.

NUTRITIONAL DISTURBANCES.—Amenorrhea may accompany severe nutritional disturbances. The mechanism is not clear but it has been shown in animals that starvation results not in decrease of gonadotropin content of the pituitary, as one might expect, but rather a normal or increased amount of gonadotropins whose release from the pituitary is in some way prevented. Whatever the mechanism, correction of the nutritional disturbance usually results in resumption of menstruation. The mechanism of amenorrhea in anorexia nervosa is more complex because of the psychogenic factors involved. In this disorder there is probably first failure of LH secretion by the pituitary and later failure of FSH secretion. Conceivably, the amenorrhea is first related to causes of emotional origin interfering with hypothalamic-hypophyseal pathways and preventing LH release while later the effect of starvation on storage or release of pituitary gonadotropins may be the important factor. In anorexia nervosa resumption of caloric intake is also accompanied by improvement in the psychiatric aspects so that it is usually impossible to determine what factor was responsible for the return of menstruation. Attention recently has been called to chronic liver disease in young women (5). In this group, amenorrhea was a common finding. Glass (19) has written of the hepatogonadal syndrome to suggest that in some women correction of menstrual abnormalities can be brought about by treatment with liver extract. These observations await confirmation.

HYPOTHALAMIC AMENORRHEA

The most commonly encountered amenorrhea is that thought to arise from disturbances of psychogenic origin in the hypothalamus. This type of amenorrhea is frequently called psychogenic and is seen in girls going away to school or college for the first time, in nurses entering training, in women separated from sweethearts or husbands as in time of war or in association with other sources of emotional stress (45). Such patients usually are normal in all respects. Vaginal smears usually show evidence of estrogen deficiency. The urinary excretion of FSH is normal

in contrast to ovarian amenorrhea where FSH excretion is high and pituitary amenorrhea where FSH excretion is low. The normal FSH levels suggest the presence of estrogen; yet in six patients reported by Klinefelter, Albright and Griswold (35) there was no bleeding on withdrawal of progesterone. To explain this observation the authors suggested that there might be a failure of the hypothalamic-pituitary nervous pathways to release LH from the anterior pituitary, and thus a condition of hypoestrinism might result. They could not explain why the lack of estrogen, as judged by failure of endometrial response, did not lead to an increased production of FSH. They suggested that perhaps the ovary was producing some hormone which itself was non-estrogenic but which might be a precursor of estrogen and which had the property of inhibiting FSH.

It has been pointed out subsequently that in a series of 29 patients with normal FSH-amenorrhea, 50% do respond to withdrawal of progesterone by vaginal bleeding (6). In such cases it is suggested that LH and estrogen have been present to some degree (good endometrial response) but perhaps not present to the extent needed for ovulation. In these cases, the type of estrogen being produced seems to be that normally produced, and FSH levels remain within normal limits.

In most instances, menstruation returns after reassurance, simple psychotherapy or resolution of the emotional difficulty. Cyclic therapy with estrogen will result in return of menstrual function in others. The duration of the amenorrhea is sometimes surprising. The author has seen one patient with psychogenic amenorrhea of six years' duration. This was seemingly in relation to a strict upbringing, a domineering mother and concern over sexual matters. When she moved to another state and became free of parental supervision, normal periods resumed.

Much less frequently organic hypothalamic lesions may produce amenorrhea. Patients with organic hypothalamic lesions usually show some evidence of pituitary disorder that distinguishes them from the psychogenic group.

Obesity and amenorrhea.—A certain number of patients with hypothalamic amenorrhea will also be obese. The association of obesity and amenorrhea has been known for some years, and it can be shown that the incidence of obesity in women with

amenorrhea is in the vicinity of 48% in contrast to the usual incidence of obesity of about 13% in a group of normal women of the same age range. Obesity is considered by many to be of emotional origin so that it is possible that obesity and amenorrhea are physical manifestations of the same emotional disorder. In animals, appropriately placed lesions in the hypothalamus will produce obesity and gonadal atrophy. About half of a given group of women with obesity and amenorrhea will be successful in weight reduction and, with weight loss, menstruation returns (38). There are two possible explanations of this phenomenon. First, the resumption of menstruation with loss of weight may be the result of the psychotherapeutic effect of interviews with physicians interested in their problem, or a negative caloric balance may, in some way, aid release of gonadotropins. Present knowledge does not permit us to distinguish between these two possibilities.

THYROID AND RADIATION THERAPY.—Before concluding this section on amenorrhea, mention should be made of the use of thyroid medication and radiation of ovaries or pituitary as therapeutic measures in the treatment of amenorrhea. It has long been claimed that thyroid is effective in amenorrhea even though evidence of thyroid deficiency is absent. In many of the studies reported, the only abnormality is a basal metabolic rate in the −10 to −20 range without other clinical or laboratory evidence of hypothyroidism. There remains no conclusive proof that in such patients thyroid is beneficial in any other way than by its psychotherapeutic effect. Studies by Buxton and Herrmann (11) have indicated that thyroid medication has no effect on amenorrhea or other menstrual disturbances occurring in euthyroid persons. Despite this demonstration, claims of the beneficial action of thyroid therapy, largely unsupported by accurate clinical observation, still appear.

Although thyroid medication in the absence of hypothyroidism is ineffective, it is not harmful. On the other hand, the use of x-ray directed at ovary or pituitary, considered by some to be beneficial in the management of amenorrhea, may be harmful in that it may produce mutation of genes. This procedure popularized by Kaplan (34) has been criticized by the geneticists so that a serious doubt as to its safety exists. There has also been recent

evidence that the clinical effectiveness of x-ray may be related to a psychotherapeutic effect. Abarbanel (1) has shown that sham treatment, where the patient thought she was receiving x-ray but was actually protected by a lead screen, resulted in resumption of menses in a significant number of cases. Such observations render claims as to the benefits of x-ray therapy less acceptable and the recent publicity regarding safe radiation exposures makes this a less attractive form of therapy.

ABNORMAL UTERINE BLEEDING

The usual duration of the menstrual period is from four to seven days. Bleeding occurring outside these limits is probably abnormal. There is considerable confusion in the terms describing abnormal bleeding and in some instances the same term may be used to express a different meaning. The terms used by Rock (46) and by Fluhmann (16) seem best in that they are descriptive. Rock prefers to restrict the term functional uterine bleeding to disorders in which there are alterations of frequency or amount of flow in ovulatory cycles. These include hypermenorrhea, hypomenorrhea, polymenorrhea and oligomenorrhea. The term dysfunctional bleeding refers to disorders of flow associated with anovulation; this is commonly referred to as metropathia hemorrhagica and is also loosely called functional uterine bleeding. Menorrhagia refers to prolonged or profuse periods following ovulatory cycles and has the same meaning but seems less descriptive than hypermenorrhea. Metrorrhagia is a more general term referring to acyclic uterine bleeding and may, therefore, include both bleeding associated with anovulatory cycles and bleeding from mechanical causes. The unfortunate term menometrorrhagia conveys little meaning.

Hypermenorrhea

Hypermenorrhea, or increase in duration or amount of flow, is sometimes difficult to assess on the information obtained from the patient but a history of change in bleeding is usually significant. Functionally, this symptom probably represents an alteration of speed of repair of the endometrium without demonstrable hormonal change. Occasionally biopsy or curettage toward the end of menstruation in patients with hypermenorrhea will show

both proliferative and secretory elements. This has been called "irregular shedding" (30). In this disorder the usual history is of regular but prolonged periods. Pregnanediol may be found in the urine after several days of bleeding and this, together with histologic evidence of mixed proliferative and secretory endometrium, suggests prolonged corpus luteum action as the etiology. More frequently, however, the patient complaining of hypermenorrhea or menorrhagia, which by definition is associated with ovulation, will be found to be bleeding from mechanical or systemic causes. This will be considered later.

Hypomenorrhea

Hypomenorrhea, or too little flow, indicates a decrease in duration or amount of flow, or both. It may be a precursor of amenorrhea and sometimes precedes the menopause and may also, of course, be associated with oligomenorrhea or too few periods. When not associated with oligomenorrhea or when occurring premenopausally it usually is of little clinical significance. Its mechanism is not clear but the endometrium, though secretory, is thinner than usually seen. Hypomenorrhea does not indicate decreased fertility.

Polymenorrhea

Polymenorrhea, or too many periods, refers to regular ovulatory cycles occurring more frequently than every 25 days. In most instances this disorder is a reflection of a shortened follicular phase. Usually the luteal or postovulatory phase of the cycle remains fairly constant. However, shortened luteal phases do occur. In some women with exaggerated bleeding at the time of ovulation polymenorrhea may appear to be present. Excluding organic pelvic disease as a cause, the clinical significance of polymenorrhea is chiefly related to the problem of infertility. In such cycles temperature charts, endometrial biopsies or pregnanediol excretion can be used as aids in determining the time of ovulation.

Oligomenorrhea

Oligomenorrhea, or too few periods, is a rather frequent disorder and is usually considered when the cycles are habitually

longer than 35 days. If each bleeding phase is similar in duration and amount it can usually be shown that ovulation has preceded the bleeding. The condition is related to and may be a precursor of amenorrhea. It is related as is amenorrhea to obesity. Possible systemic or psychic causes should be considered. It is chiefly of clinical importance in relation to infertility, where it becomes difficult to advise as to when ovulation is occurring.

Dysfunctional Uterine Bleeding

The above conditions—hypermenorrhea, hypomenorrhea, polymenorrhea and oligomenorrhea—are related to disturbances in frequency or duration or amount of flow in ovulatory cycles and are best called functional disorders. When abnormal bleeding is associated with lack of ovulation, the condition is called dysfunctional uterine bleeding or, more commonly, metropathia hemorrhagica. As mentioned before, it is less properly called functional uterine bleeding. The condition is related to and may be associated with amenorrhea and is presumably due to a decreased or normal amount of estrogen acting for too long in the absence of progesterone. Since progesterone production depends on the release of sufficient luteinizing and probably luteotropic hormone, the essential defect is thought to be a disturbance in the normal reciprocal relationship between pituitary and ovary. Metropathia, because it represents anovulatory bleeding, occurs most frequently at the menarche, when ovulation has not yet been regularly established, and at the time of the menopause, when regular ovulation becomes less frequent. Usually the cycle is grossly irregular, the bleeding may be preceded by amenorrhea, the periods are painless and the bleeding is excessive or prolonged. Curettage or biopsy will almost always show a proliferative endometrium and there may be endometrial hyperplasia. Increasingly in women with bleeding thought to be dysfunctional a history of receiving estrogens either by mouth or parenterally may be obtained. Rarely, in a patient with acyclic bleeding, a secretory endometrium may be obtained representing, in most instances, a chance ovulation in a patient with true metropathia.

The irregular and profuse nature of the bleeding in metropathia will usually permit its distinction from functional bleeding associated with ovulation where the periods are regular or else

are similar to one another in amount and duration. However, the separation of metropathia from other causes of acyclic bleeding requires a consideration of these causes, and in this sense the diagnosis of metropathia is one of exclusion. There are numerous classifications of abnormal uterine bleeding and it has been found convenient to consider the causes on an etiologic basis (50), namely: (1) functional and dysfunctional bleeding, (2) mechanical causes, (3) aberrations of pregnancy, (4) systemic causes and (5) miscellaneous causes. The first group has been discussed.

Under mechanical causes are grouped benign and malignant tumors of the uterus and cervix, polyps and cervical erosions. It seems reasonable to assume that the abnormal bleeding found in association with benign disorders is due to mechanical interference with blood supply and in the case of malignancies is related to erosion into the capillary bed. It must be pointed out, however, that more than one cause of abnormal bleeding may be present, and the demonstration of a uterine fibroid does not necessarily mean that the fibroid is causing the bleeding, the true cause perhaps being functional or systemic. Unfortunately, the history does not permit us to distinguish the cause of the hemorrhage, but in bleeding from mechanical abnormalities one is more likely to be able to pick out recognizable periods, or a history of intermenstrual spotting may be obtained. Cramps may be present, suggesting ovulation.

It is usually possible to recognize aberrations of pregnancy when confronted by abnormal bleeding. The young woman with a previous history of regular painful periods, who suddenly has excessive or prolonged vaginal bleeding after an episode of amenorrhea, is likely to be bleeding from causes associated with pregnancy, namely, miscarriage either spontaneous or induced, or an ectopic pregnancy. One must exclude the relatively rare hypofibrinogenic and fibrinolytic mechanisms.

It is customary to consider such blood dyscrasias as idiopathic thrombocytopenic purpura, leukemia and aplastic anemia as causes of abnormal vaginal bleeding. Some patients with these disorders will have excessive or prolonged menstruation. The mechanism of excessive bleeding in these disorders is not clear and it should be pointed out that most women with these dis-

orders do not have difficulty with menstruation. It has been shown that frequently a primary gynecologic disorder may also be demonstrated in women with systemic hemorrhagic disorders (3). The administration of heparin or Dicumarol® to normal women usually does not result in excessive vaginal bleeding. The management of the patient with excessive vaginal bleeding and a systemic vascular disease varies with each patient and care must be taken to consider more than one cause. As a general rule, it seems logical first to direct one's attention to the systemic disorder to avoid uncalled-for curettages or, even more tragic, an unnecessary hysterectomy. Some women with aplastic anemia or thrombocytopenia of various origins experience a decrease in vaginal bleeding when given cortisone. This may occur without change in platelet counts and is presumably due to increased vascular resistance (12).

In recent years, it has been claimed that in the blood of some women with menorrhagia there can be shown an increase of heparin-like substances as reflected by protamine titration. This has been offered as an explanation of some instances of abnormal bleeding (14). Toluidine blue and protamine sulfate are said to correct the hypocoagulability of the blood and the menstrual disturbance. The initial reports of the use of these substances were probably too enthusiastic. In cases of uterine bleeding with positive protamine titration toluidine blue seems to be effective but in uterine bleeding secondary to endocrinologic disturbance, organic pelvic disease or endometrial dysfunction it is of no value (8).

Parenchymal liver disease has been claimed to be causally related to menstrual disturbances. In liver disease, alteration of both estrogen and progesterone metabolism occurs. In some but not all patients with hepatic disease, interference with conjugation of estrogen and progesterone can be demonstrated. In others with equally severe liver damage, no such abnormality seems to be present. It would seem logical that in a patient with liver disease and increased circulating estrogen menorrhagia might well occur. Biskind and Biskind (9) advanced the concept of liver deficiency on a nutritional basis as a causative factor in menorrhagia and other menstrual disorders and reported improvement of the menstrual abnormalities after admin-

istration of vitamin B complex. However, a critical review (24) of the problem throws this theory into question and the observations of Pincus and his co-workers (42) suggest that the major disturbance in such patients is a pituitary depression independent of hyperestrogenism.

In some instances of pelvic inflammatory disease, excessive or irregular menstruation is found. There are no good clinical observations as to the mechanism of bleeding in such patients. It presumably could be due to mechanical interference with follicular development and ovulation but no data on this are available. Equally obscure is the mechanism of abnormal bleeding that sometimes occurs in patients with endometriosis. A certain number of women with myxedema will show acyclic uterine hemorrhage. Goldsmith *et al.* (20) have shown that the bleeding is associated with anovulatory cycles and once the myxedema is treated regular ovulatory menstruation resumes.

Whereas psychogenic amenorrhea appears to be a clinical entity with an acceptable theoretical explanation, the concept of excesses of bleeding due to psychogenic causes must be approached with more caution and accepted more hesitantly. Again, not many thorough studies of such patients are available. The association of unexpected bleeding with severe stress or fright is fairly common but in such an apparent instance one must exclude other more likely causes of bleeding. However, it seems clear that abnormal uterine bleeding may be associated with psychogenic causes. Depression may be one of the more prominent stimuli (28). Women with hysteria will frequently describe prolonged or excessive or irregular bleeding. One clinical point of importance is that the woman with hysteria and complaining of what appears at first to be irregular anovulatory bleeding will frequently also complain of severe cramps with each period. Such a history should make the physician suspicious of the diagnosis of hysteria. Usually, enough other symptoms will be present to establish the diagnosis and cause the physician to consider the need for curettage or other gynecologic procedures as of less vital importance. On the other hand, it must also be pointed out that the woman with hysteria is not immune to the other causes of abnormal bleeding.

Granulosa cell tumors and theca cell tumors which may occur

both before the menarche and after the menopause should be considered in differential diagnosis.

MANAGEMENT OF METROPATHIA HEMORRHAGICA.—The diagnostic study of the woman with abnormal bleeding should include a thorough history, physical examination and pelvic examination. Vaginal smears are helpful in estimating estrogen activity. Blood smears, bleeding and clotting time, prothrombin time, clot retraction and tourniquet test will usually bring to light systemic vascular disorders. Before accepting the diagnosis of metropathia, curettage should be performed in older patients. If an aberration of pregnancy is suspected, curettage in younger women should be done.

Once it is established that the problem is that of metropathia hemorrhagica, several courses of action are possible. Where curettage has been done, this diagnostic procedure alone may prove all that is necessary for treatment in about one third of the cases.

The usual method of control of metropathia consists of the administration of estrogen or progesterone singly or combined. In women with excessive bleeding when first seen and in whom rapid cessation of bleeding is necessary, one can effect hemostasis by the use of estrogen by mouth. Stilbestrol, 6 mg. a day will frequently stop bleeding in 36 to 48 hours but larger doses may be required. Its administration should be continued for at least 25 days, since its withdrawal will again produce bleeding. The estrogen is stopped at the end of 25 days and bleeding occurs usually within six to seven days. After three or four days of bleeding, stilbestrol, in doses of 1.0 mg. daily, is used in the same manner until three controlled cycles have occurred. It is, at this point, advisable to give no further medication until an opportunity has occurred to see what sort of cycle the patient will have by herself. When using estrogen as described there may be some advantage in giving progesterone on days 21 to 25 with the hope that withdrawal of both hormones simultaneously will provide for a "cleaner shedding" of the endometrium. Recently, intravenous Premarin® (22) has been shown effective in producing rapid hemostasis. Its initial use intravenously should be supplemented by oral medication for the remainder of the 25 days as described above. In some instances of metropathia, when bleeding is not

excessive, progesterone alone may be used. The demonstration by vaginal smear of adequate estrogen levels can be used as a guide as to whether progesterone will be effective. In such patients, when progesterone is given and withdrawn, bleeding continues for a few days, the effect of the administered progesterone being to elevate and then lower blood progesterone levels so that an episode of progesterone withdrawal bleeding occurs. The progesterone can then be administered at five-week intervals and with resultant episodes of withdrawal bleeding. It is helpful to wait the five or six weeks in the hope that normal ovulation and menstruation will occur during this time. Progesterone can be administered intramuscularly in doses of 5 or 10 mg. daily or by buccalet in doses of 40 to 50 mg. a day. Larger doses are frequently necessary. Testosterone is also effective in the hormonal control of metropathia and can be given either intramuscularly or orally. Its mechanism of action is not clear but may be related to a progestational effect or a direct effect on the endometrium.

The success of hormonal control is variable and controlled withdrawal bleeding may have to be continued for some months or even years. Hysterectomy or castration in young women with metropathia should, of course, be considered only as a last resort.

DYSMENORRHEA

Some form of abdominal distress, most commonly lower abdominal cramps, is the normal accompaniment of menstruation. Why ovulatory menstruation should be associated with some discomfort is not clear. Normal healthy young women may experience some discomfort usually for a few hours on the first day of menstruation and accept it as a normal event. A few women experience sufficient distress to cause them to lose time from work or school and to interfere with their usual activities. Statistics as to the incidence of dysmenorrhea show wide variation, due to different definitions and to inclusion of women with relatively mild discomfort. The frequency of dysmenorrhea requiring a day in bed is probably between 3 and 15%. It has been said that one should not call painful menses dysmenorrhea unless the patient consults a physician.

There are many classifications of dysmenorrhea. The terms secondary or extrinsic refer to painful menses due to some path-

ologic state within the pelvis, while primary or intrinsic dysmenorrhea refers to pelvic pain not associated with any demonstrable pelvic disease.

The more common causes of secondary dysmenorrhea are pelvic inflammatory disease, endometriosis, adenomyosis and uterine fibroids. Chronic congestion of the pelvis is offered as a cause but the specificity of this disorder as a clinical syndrome is not clear. The pain with these disorders is thought to be due to mechanical interference with uterine contractions. Not all patients with such pelvic disorders experience dysmenorrhea and the demonstration of a pelvic abnormality does not provide conclusive evidence that it is necessarily the cause of the pain. Once considered a common cause, displacements of the uterus are seldom thought to be of importance in the production of dysmenorrhea.

In most women with painful periods no pelvic disease is demonstrable and such women are considered to have primary or intrinsic dysmenorrhea. Although cramps are usually the presenting symptoms, headaches, irritability, backache and gastrointestinal disorders are frequent accompaniments.

The mechanism of the pain in primary dysmenorrhea has been the subject of much study. Bickers (7) postulated that dysmenorrhea is due to hypertonic dysrhythmic uterine contractions, and that this disordered mechanism could be the result of vasoconstriction. Moir (39), using intrauterine balloons, showed an exaggeration of uterine contractions in women with dysmenorrhea. The peak of uterine contractions coincided with the intensity of the pain and with obliteration of pulsations of the uterine artery. Woodbury (59) found increased tonus between uterine contractions and demonstrated disorderly uterine contraction in association with dysmenorrhea. Diehl and Hundley (13), however, failed to confirm these observations, finding no difference in the uterine tracings of women with dysmenorrhea as compared with a group of normal women.

A number of theories as to excess or deficiency of estrogen or progesterone or imbalance of these hormones have been offered to explain dysmenorrhea but they remain speculative and unproved. By some, insufficient estrogen is thought to result in disturbances of the sympathetic nervous system. A deficiency of

corpus luteum hormone as a cause of dysmenorrhea is hardly acceptable because normally, premenstrually, there is degeneration of corpus luteum and decrease in pregnanediol excretion. Theories as to an imbalance of estrogen and progesterone arose from work in the rabbit demonstrating that estrogen stimulates uterine contractions while progesterone inhibits such contraction. It was postulated that dysmenorrhea results from an excess of estrogen or a deficiency of progesterone. There are several objections to this theory. Other investigators have not been able to show the quieting effect of progesterone on uterine activity. Painful periods are almost always associated with ovulation and progesterone secretion, and the bleeding of anovulatory menstruation in which estrogen acts unaided by progesterone is characteristically free from pain. An excess or prolongation of progesterone secretion has been postulated in so-called membranous dysmenorrhea but abnormal corpus luteum activity has not been demonstrated in the usual type of dysmenorrhea.

Generally it can be shown that primary dysmenorrhea is associated with psychogenic causes (27). The diagnosis is based not only on the exclusion of mechanical causes but on positive evidence of psychogenic factors. It can be shown that women with dysmenorrhea have a lower pain threshold than normal women. As a group, women with dysmenorrhea have been shown to have increased frequency of emotional maladjustment in childhood. As adults, they may have a deep resentment of their feminine role or may be chronically anxious and complaining. Many women with dysmenorrhea will, however, show no evidence of emotional instability. In many instances young women have been led to believe that their pain is abnormal or have received from friends, or more often from their mothers, erroneous concepts of menstruation. The terms "the curse," "being unwell" or "the sickness" do not help in establishing in the mind of the adolescent that menstruation is a normal process.

The management of the patient with dysmenorrhea should include, obviously, a complete history, physical examination and an adequate pelvic examination to exclude mechanical causes. As mentioned above, if local pelvic abnormalities are found, one must be alert to the possibility that such disorders may still not be the explanation of the patient's complaints. The management

of uterine fibroids and endometriosis is not within the scope of this paper but if surgery seems necessary every effort should be made to provide continuation of the child-bearing function.

The history is of importance in evaluating the patient who appears to have primary dysmenorrhea. Menses that are painful from the onset of the menarche when ovulation is not frequent suggests a psychoneurotic factor. Women who have pain lasting more than one day are also likely to have other psychoneurotic manifestations.

In the treatment of primary dysmenorrhea, a simple explanation of the mechanism of ovulatory menstruation along with the assurance that it is a normal event will, in many instances, suffice. Some will be helped by simple non-narcotic analgesics. Should these measures fail, the next logical procedure is an attempt at suppression of ovulation. Sturgis and Albright (54) showed that if ovulation were suppressed by an estrogen, a painless period would result. The usual procedure is to administer 1.0 mg. of stilbestrol daily for 21 days, starting on day 1 of the cycle. In some women, a larger dose is necessary and a convenient schedule is 1.0 mg. a day the first week, 2.0 mg. a day the second week and 3.0 mg. a day the third week. In most women, the resulting bleeding will be free from pain. If there is no relief, one is usually dealing with a psychoneurosis requiring further psychiatric study. The suppression of ovulation by such methods appears to be harmless. It is not advisable, and indeed it is probably impossible, to suppress ovulation for more than two cycles in a row. In many instances, the demonstration that something can be done for the patient is of considerable psychotherapeutic benefit. Testosterone has been used in the management of dysmenorrhea. Given early in the cycle, its effect is probably to suppress ovulation. Given later in the cycle, the mechanism of its action is not clear but it may be related to a progestational effect. Recently, a nonsteroidal ovarian hormone acting as a uterine relaxant has been reported effective (32). The large number of preparations reported in the literature and presented in advertisements to physicians with "good results" reported in about 75% of the cases, no matter what is given, attest to the fact that the major action of medications is psychotherapeutic. The physician who takes the time to listen to his

patient, to explain the mechanism of dysmenorrhea and, above all, to reassure her will in most instances find a simple program to be of benefit. In a few instances, surgical measures may be necessary. Procedures such as dilatation of the cervix and insertion of stem pessaries are fortunately rarely used today. The most commonly used surgical technic is that of presacral neurectomy, which should be used only as a last resort and is reportedly successful in 50 to 90% of patients.

PREMENSTRUAL TENSION

Closely allied to dysmenorrhea is the syndrome of premenstrual tension. The term is usually applied to a wide variety of symptoms occurring for several days before menstruation. The more common complaints are a sense of abdominal bloating or discomfort, backache, headaches, increased nervousness or tension, depression, irritability, insomnia, dizziness and mastalgia. The headaches usually described consist of pain or pressure on the top of the head or back of the neck. Women with migraine or vascular headaches have them more frequently before the menses, but after careful questioning they will often admit to having similar headaches at other times of the cycle as well.

Many women experience one or more of the symptoms of the premenstrual tension syndrome and yet are not sufficiently disturbed to complain to physicians. In others, the complaints are sufficiently troublesome for them to seek help. There occurs then a fine distinction as to the point where the symptoms progress from the physiologic to the pathologic. Because of this, it is difficult to delineate a clearly defined and recognizable syndrome.

During the premenstrual phase in normal women, there is retention of water, sodium and chloride. This is reflected in gain in weight of from three to ten pounds and there may be recognizable generalized edema. Studies by Thorn and his co-workers (56) indicate that the sodium-retaining properties of estrogen and progesterone are responsible for premenstrual retention of water and electrolytes. There is increased evidence that adrenal corticoids play an important role in the production of premenstrual edema. At the onset of menstruation, diuresis, loss of weight and disappearance of edema occurs.

Earlier theories related the symptoms of premenstrual tension

to imbalance of estrogen and progesterone. Greenhill and Freed (25), however, suggested that the syndrome was due to retention of sodium and water and advocated salt restriction and ammonium chloride as diuretic measures. This method, or modifications of it, is in general use for relief of premenstrual tension symptoms. There is no general agreement as to the relationship between the severity of the symptoms and degree of retention of water and electrolytes.

It, however, remains difficult to understand why what appears to be a normal accompaniment of the menstrual cycle and in most women not sufficiently distressing to cause complaint should, in some women, assume the dignity of a pathologic entity. The symptom of backache, headache and irritability occur in many such women without evidence of much weight gain, and dehydration measures do not always relieve tension and irritability (44). Many women with premenstrual tension have either past or other present symptoms indicative of psychoneurotic patterns and are helped or relieved entirely by simple psychotherapy and mood-elevating drugs given premenstrually. Psychiatric studies of emotional content of women during various phases of the menstrual cycle indicate that depression of varying degree is common before the menses and it seems logical to consider the symptoms of the premenstrual tension syndrome as an exacerbation in susceptible or over-reactive women of a physiologic process. From a practical point of view, reduction in salt intake, reassurance and mood-elevating drugs during the premenstrual phase will be helpful in most instances.

THE MENOPAUSE

The menopause is a normal event signifying the end of reproductive function. It may occur at any time from ages 40 to 55 with an average age of onset of around 48. There is evidence that the menopause is occurring progressively later. In ancient times it occurred at about age 40. From 1500 to 1830 it occurred at about age 45 while today the average age is probably 48 or 49. The first events to occur are decreasing frequency of ovulation and decreasing estrogen production. As a result, menstrual periods may suddenly cease or more usually become irregular. They may become profuse or prolonged. With decreasing pro-

duction of estrogen, the urinary levels of FSH and LH rise. This may occur prior to cessation of menstruation. The symptoms of the menopause that are hormonally mediated are amenorrhea and vasomotor instability as manifested by hot flashes. Increased pituitary secretion of gonadotropins is implicated in the production of the hot flash, although the mechanism is not clear. Estrogens are known to affect arterioles and venules and it may be that the hot flash is mediated through this mechanism. The large number of other symptoms, irritability, palpitations, dizziness, parasthesias, emotional instability, depression, insomnia, fatigue, jealousness and self-deprecation, are manifestations of psychologic problems occurring in midlife (48). These symptoms are not produced by lowered estrogen levels and there is no evidence that they are relieved by administration of estrogen.

The available statistics indicate that between 10 and 15% of women will seek medical advice at the time of the menopause, most adjusting without sufficient symptoms to produce distress. Anxiety and depression usually produce the symptoms that send the patient to the physician. At about midlife a woman finds her role in the family circle undergoing a change. Her children are usually grown and have developed interests outside the home, creating in the mother a sense of no longer being needed. Lack of fulfillment of social aspirations and disappointment in her children may present problems. Some women feel that their useful years are ended with the loss of reproductive capacity. They may fear cancer, obesity or insanity. Many women are poorly prepared for these conflicts, and anxieties and depression may result. It is of significance that women with psychoneurotic symptoms at the menopause will usually be found to have had psychoneurotic symptoms at a previous time. Women with a long history of dysmenorrhea are likely to have a difficult menopause.

The physician must determine that the symptoms presented are actually related to the menopause and not due to some underlying nonrelated disease. Tragedy can result if all complaints arising at midlife are casually assumed to be due to the menopause. Once it is established that the symptoms are menopausal, most patients can be greatly relieved by reassurance, rational explanation of the event and simple psychotherapy.

Although hot flashes can be considerably helped by simple reassurance or sedation, the accepted treatment of hot flashes is the proper administration of estrogen. When estrogens are used they should be given in small oral doses on a definite cyclic schedule so that if withdrawal bleeding occurs it reasonably can be attributed to the administered estrogen and not an unrecognized uterine malignancy. It is the general custom to give an estrogen for 30 days, stop for seven days and then resume this cycle. Such schedules usually relieve hot flashes satisfactorily. Within a few months most patients can be weaned from the medication.

Opposition to the use of estrogens is based on the thesis of interference with a normal event, postponement of an eventual physiologic adjustment and the possible carcinogenic effect of estrogens. There is no general agreement that estrogens do postpone an adjustment or that, if they do, it is necessarily deleterious. The possible carcinogenic effect of estrogens has led to warnings against their use but it remains unlikely that estrogens as used therapeutically are carcinogenic. The arguments about prolongation of the menopause and carcinogenicity of estrogens are probably not vital when short-term therapy is concerned.

The larger problem relates to whether or not estrogens should be used over prolonged periods. There is evidence to suggest that dermal and genital atrophy, atherosclerosis and osteoporosis in postmenopausal women may be prevented or delayed by estrogen therapy. The fact that life expectancy of women in the past 50 years has increased from 48.7 years to 72.4 years renders the problem of whether or not to advise prolonged estrogen therapy more than an academic one.

The major objection, of course, to such a suggestion relates to the problem of carcinogenicity of estrogens. It is known that in mice, estrogens can produce cancer. There is in humans an apparent relationship between endometrial hyperplasia, a reflection of hyperestrogenism and endometrial malignancy. There is evidence of an increased frequency of association of feminizing tumors and endometrial malignancy and there is an apparent association between ovarian stromal hyperplasia and malignancy of breast and uterus. There are also several individual case reports in which administration of estrogens has coincided with the development of malignancies of breast and reproductive

tract. Larson (36) has critically reviewed the evidence and pointed out the wide discrepancy of views concerning the relation of hyperplasia and endometrial carcinoma, concluding that there is no large series to show that the co-existence of these two entities is any greater than could be expected on the basis of chance. He felt that the co-existence of feminizing tumors and breast and reproductive tract malignancies could well be a reflection of high incidence of multiple lesions seen in many cases of cancer. Larson criticized the association of ovarian stromal hyperplasia and endometrial carcinoma on the basis that the control groups used were not true controls. An additional bit of evidence is that there was no change in the incidence of cancer of the breast and sex organs in 1950 when estrogens were widely used as compared to 1930 when estrogens were rarely used.

A large series of patients observed for a long time is needed to determine whether the possible advantages of long-term estrogen therapy in mitigating the onset of genital atrophy, osteoporosis and cardiovascular changes outweigh the possible risk of producing endometrial or breast carcinoma. It seems reasonable to say that the concern over the use of estrogens does not seem justified by the evidence available. There remains no direct proof that estrogens are carcinogenic when used therapeutically and the circumstantial evidence has been seriously challenged.

In recent years, androgens alone or more commonly in combination with estrogens have been advocated in menopausal therapy more or less empirically. The advantages of combined therapy appear to be a synergistic effect on pituitary suppression and the protein anabolic effect of androgen that presumably results in a sense of well-being and an increase in libido. The use of androgen permits a smaller dose of estrogen and decreases estrogen-induced bleeding. Combined therapy seems indicated in women with osteoporosis and in those in whom estrogen-induced bleeding is a problem as well as in women with chronic cystic mastitis associated with the menopause. In order to avoid masculinization the total dose of testosterone propionate or its equivalent given parenterally must be less than 300 mg. a month.

Abnormal uterine bleeding at the time of the menopause is relatively frequent and is associated with lack of regular ovulation. As mentioned above, almost any variant of abnormal bleed-

ing may be encountered. When presented with a patient who has had one episode of prolonged or profuse bleeding, and careful physical and pelvic examination including cytologic study have excluded systemic or local causes, it is generally safe to wait at least until another cycle has been observed. A second abnormal period is usually an indication for curettage to exclude the ever-present possibility of uterine malignancy. If malignancy is excluded and bleeding persists, control with hormones can be attempted. Usually, in menopausal bleeding, insufficient estrogen stimulation is occurring for progesterone to be as effective as it is in functional bleeding before the menopause. Usually, one has to give estrogen such as stilbestrol 1.0 mg. daily for 25 days with progesterone on days 20 to 25. This cycle is repeated for two to three months and then discontinued in the hope that further abnormal bleeding will not occur. Frequently, curettage alone suffices to relieve the complaint. Hysterectomy to control menopausal bleeding in the absence of demonstrable mechanical abnormalities is rarely justified.

Postmenopausal bleeding, namely, bleeding occurring more than one year following apparent cessation of menses, is a clear indication for curettage and delay in performing this is not justified. Unfortunately, the type of bleeding experienced does not permit a distinction between bleeding from benign or malignant causes.

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